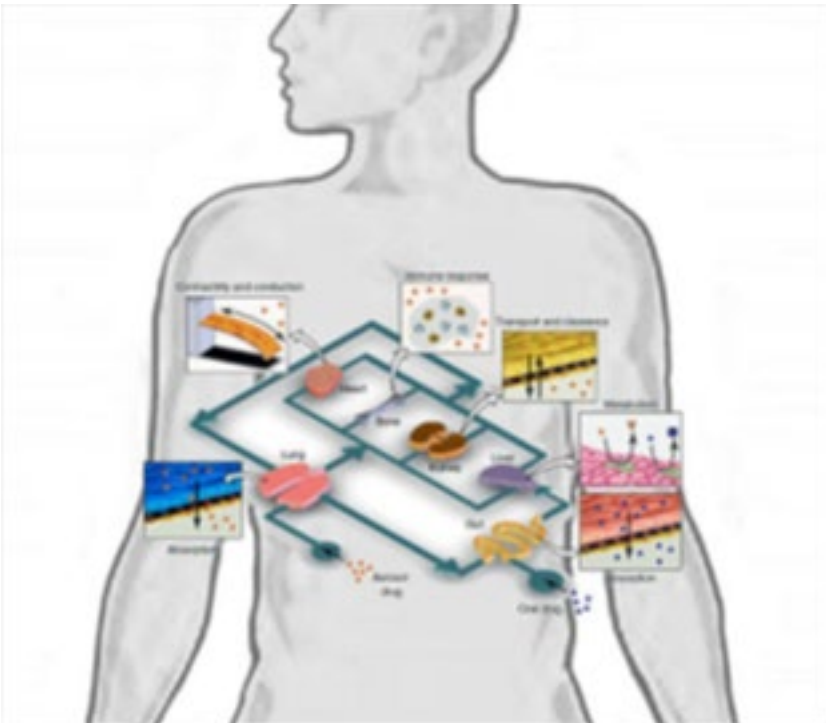

Image by Timothy.ruban, available under a Creative Commons Attribution-Share Alike 3.0 Unported license.

March 14-15, 2013
LISTER HILL AUDITORIUM
NIH CAMPUS, BETHESDA, MD

REPORT ON
THIRD WORKSHOP ON VALIDATION AND QUALIFICATION OF NEW IN VITRO TOOLS AND MODELS FOR THE PRE-CLINICAL DRUG DISCOVERY PROCESS

American Institute for Medical and Biological Engineering

NIH National Institute of Biomedical Imaging and Bioengineering

M-CERSI

Executive Summary

The third AIMBE/NIH workshop on validation and qualification of new in vitro tools and models for the pre-clinical drug discovery process was held on March 14th and 15th at the NIH Campus in Bethesda, MD. The overall goal of this series of workshops is to develop guidelines for investigators developing new pre-clinical drug development models on how to validate and qualify these new technologies so that they become useful, meaningful tools qualified by the FDA. The workshop was able to generate specifics for validation and qualification of new in vitro systems based upon the more broadly developed groundwork achieved in the first two meetings.

Validation defines the information generated before submission to the FDA and the meeting initiated the process of clarifying the broader definitions necessary for integration of new platform technologies into pre-clinical safety evaluation. These new validation definitions include acute and chronic categories for device application for toxicity testing and safety evaluation. The role of efficacy at this stage was also discussed but it was agreed this was complicated and needed further clarification. However, what was universally agreed upon was that lists of compounds need to be determined for each of these sub categories, and any additional categories, for the community to use in generating the data to seek broad validation.

For qualification, it was determined that these systems need to be evaluated in terms of safety and toxicology for pre-clinical applications and then separately for efficacy. The group also concluded that qualification should be sought for broad context of use, beyond a single IND, which currently is not something that the FDA, and especially CDER, is familiar with in current applications. In fact, the representatives for CDER indicated that there are currently no guidelines for qualification of these systems. However, they will be willing to utilize findings and input from these Workshops as part of the basis for future guidelines for these systems. Taken together this is a major advancement for defining the steps necessary for getting these technologies ready for evaluation for use in the pre-clinical drug discovery phase during drug development.

There were approximately 140 people in attendance including 8 AIMBE fellows and representatives from government agencies (NIH, NIST, DoD, FDA, HSS), academia, and the private sector. A detailed report and draft agenda for the next meeting to be held at NIH on November 6 and 7th follows this summary.

Report on the Third AIMBE/NIH Workshop on Validation and Qualification of New In Vitro Tools and Models for the Pre-clinical Drug Discovery Process
March 14 -15, 2013
NIH Campus, Lister Hill Auditorium

Dr. J. Hickman welcomed the attendees and went over the results from the last workshop and goals of the current workshop, which was to further define validation and the subsections of qualification, toxicology and efficacy. He also pointed out the differences between in vitro systems for clinical outcomes, which is in CDCH, and for pre-clinical drug safety evaluation which is in CDER.

The workshop was divided into four sessions which are summarized below.

Session 1: Current Government Perspectives on Validation and Qualification of New In Vitro Tools and Models for the Pre-Clinical Drug Discovery Process
This session highlighted the viewpoints of Industry, the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA). The presenters included Federico Goodsaid, PhD, Vertex Pharmaceuticals, Sonja Beken, PhD, European Medicines Agency, and Thomas Colatsky, Ph.D., CDER, FDA.

- Dr. Goodsaid stressed that for qualification of a new technology there is great need to clearly define the context of use. Once a tool is qualified, that means that analytically valid measurements using it can be relied on to have a specific use and interpretable meaning. Further details are at http://www.nibib.nih.gov/sites/default/files/S1_Federico-Goodsaid_0.pdf

- Dr. Beken presented information on the EMAs 3R's policy. The 3 Rs are replacement, reduction and refinement as related to regulatory testing of medicinal products in Europe. She spoke about the joint ad hoc committee to identify opportunities to implement 3Rs in the regulatory arena and to provide a concept paper for the replacement of animal studies for in vitro models. Dr. Beken's presentation can be viewed at http://www.nibib.nih.gov/sites/default/files/S1_Sonja-Beken.pdf

- Dr. Colatsky presented FDA's point of view on the topic. He said that FDA is supporting efforts to reduce the use of animals in testing. He introduced CDERs current guidelines for qualification of drug development tools but pointed out that to date they do not apply to in vitro model systems, but CDER was willing to use the report from this and future workshops as a part of the basis for guidelines for this technology. Dr. Colatsky's presentation can be found at http://www.nibib.nih.gov/sites/default/files/S1_Colatsky_0.pdf

Session 2: In Vitro Technologies for Draft Validation Guidelines
The second session consisted of a series of talks on new, cutting edge, in vitro pre-clinical drug discovery tools that have been, are in the process of, or need to be, validated and qualified for use in pre-clinical drug discovery.

- Dr. Margaret Sutherland, NIH co-Director of the Microphysiological Systems Program (MPS), spoke about the current progress. She emphasized the need for advancing regulatory science to improve the current system for drug and vaccine development. The NIH approach to developing model 3D tissues is to develop microsystems that are physiologically accurate, genetically diverse, and pathologically representative.

- Dr. Kyle Kolaja, Cellular Dynamics International (CDI), discussed the work of CDI to develop iPS

cell-derived tissues and their role in developing novel assays for drug discovery. Currently cardiomyocytes, neurons, hepatocytes and endothelial cells are available and under the CDI warrantee Dr. Kloaja's talk can be found at http://www.nibib.nih.gov/sites/default/files/S2_Kolaja.pdf

- Dr. Jonathan Himmelfarb, University of Washington, presented a tissue engineered human kidney microphysiological system that his group is developing. He spoke about the need for developing a kidney on a chip due to the increased incidence and prevalence of kidney disease. The kidney chip could lead to improved drug dosing, tools to understand uremia, improving kidney transplantation, improved drug development and a step toward a wearable kidney device. More information on this talk is at http://www.nibib.nih.gov/sites/default/files/S2_Himmelfarb.pdf

- Dr. Brett Blackman, Chief Scientific Officer of HemoShear, LLC, was the fourth speaker of the session. His company has developed two human system models, vasculature and liver, as a tool for drug development.

Session 3: Development of Draft Validation Guidelines

Session 3 consisted of a series of presentations of current research being conducted under the NIH/DARPA/FDA Microphysiological Systems "human on a chip" Program.

- Dr. Tom Hartung, Johns Hopkins, presented a 3D model of human brain for use as an improved method to animal models for developing drugs and medical countermeasures to bioterrorism. Dr. Hartung approached the issue of how to move away from the "gold standard" of animal testing to in vitro testing to evaluate safety and toxicity and stressed that evidence-based toxicology should be used including mechanistic rather than correlative validation. More information on this can be found in his presentation at http://www.nibib.nih.gov/sites/default/files/S3_Hartung.pdf

- Dr. George Truskey, Duke University, spoke about the development and use of a circulatory system with integrated muscle tissue for drug and tissue toxicity. The function/physiology of the model is being evaluated systematically throughout the development process to provide validation of the system. Toxicity testing with agents such as statins is also ongoing. His presentation can be found at http://www.nibib.nih.gov/sites/default/files/S3_Truskey.pdf

- Dr. Kevin E. Healy, University of California Berkley, described a disease-specific human tissue microphysiological model on a chip that his group is developing using patient iPSCs. These hiPSCs can be differentiated into multiple tissue types for evaluation. The platform being developed allows for real-time sampling including ELISAs, mAb arrays, Raman microscopy, mass spec, metabolism assays, and electrophysiology. He suggested that the validation process will look to model normal physiological activity and responses to different drug and disease models. Further information is available at http://www.nibib.nih.gov/sites/default/files/S3_Healy.pdf

- Dr. Karen Hirschi, Yale University, presented an integrated heart-liver-vascular system model for drug testing. The integration of multiple organ systems will allow for disease modeling that may impact multiple organ systems concurrently. The plug and play bioreactor has long term goals of being a modular platform, providing perfusion as well as electrical and mechanical stimulation, portable, allowing for real time imaging, and allowing for the long term culture of organ systems.

- Dr. Lansing D. Taylor, University of Pittsburgh, presented research on a 3D biomimetic liver platform for predicting toxicity in humans. In addition to recapitulating liver physiology, his goal is to develop

a predictive drug database. He stressed that validation of the components and the complete system is paramount. More information may be found at http://www.nibib.nih.gov/sites/default/files/S3_Taylor.pdf

Session 4. Parallel Breakout Group Discussions of Validation and Qualification for Test Case Technologies

Following session three, the workshop broke out into groups to discuss the validation and qualification of three different technology platforms that were presented earlier in the meeting: HemoShear (Brett Blackman), Berkeley (Kevin Healy), and Pittsburgh (Lansing Taylor). The breakout sessions were structured to allow for direct interactions between the technology developers and the audience in a dynamic environment.

- The HemoShear discussion was led by Dr. Luke Lee. The developer of the technology stated that scientific (biology and functionality) validation of the technology had been completed and published. The company needed to show that the in vitro system matched the in vivo biology including organ, tissue and regional specific biology. There has not been any independent validation of the technology. The developer thought that was nearly impossible to do because of the complexity of the system. As for qualification, the developers did not see a need for it. The company is using the system as a service to drug company clients rather than as a product to be purchased by drug companies. Instead, it is a better business model to address the customer (pharmaceutical companies) needs for these tools. Industrial validation is accomplished through testing a known set of compounds to see how the technology performs.
- The discussion of the Berkley Technology Platform was led by Dr. Warren Grundfest. Their session agreed that the move away from animal testing to in vitro technologies in one step will not work. Instead, the community must work with multiple methods using reference compounds to investigate in vitro models. The breakout session also discussed how to address both acute and chronic issues, and the need for multiple organ systems. In addition, separation of the applications should be made into toxicology and efficacy. The session concluded by discussing whether stem cells can be accurately used to predict the response from genetic variations as well as age.
- The discussion of the Pittsburgh Technology platform was led by Dr. Michael Schuler, Ph.D. That breakout group concluded that pharmaceutical companies are not sufficiently involved; that to be successful the design of in vitro technologies must include the consumer. Also, the initial steps of technology development are integral to success including standardization and quality control before validation and qualification. They must first test well-known and characterized reference drugs before continuing to validation and qualification.

Lessons Learned

Following the meeting, the organizers and co-sponsors sent out a survey to meeting participants to get feedback on the structure and content of the workshop. Approximately 40 attendees responded to the electronic survey. A few common trends in the results were the following:

- The content was great- many individuals commented on enjoying the technical sides of the presentations and the facility.
- Many individuals commented on how helpful the breakout sessions were in tying together the major themes of the workshop.
- A number of respondents felt the perspective from the FDA was very important in continuing discussions on validation.

Going forward, it was recommended that:

- The workshops include input from the pharmaceutical industry and NCATS.
- Prospective attendees are given more advanced notice of the workshops, to invite colleagues.

Next Steps

The Workshop Steering Committee has had two teleconference calls since the March meeting to review the outcomes of the Workshop and to begin to plan the 4th Workshop in the series. The committee added one additional member, Dr. Khaled Bouri, from the Office of the Commissioner, FDA. The committee now consists of the following members:

- Sonja Beken, PhD, Belgian Federal Agency for Medicines and Health and the European Medicines Agency
- Khaled Bouri, PhD, Office of Critical Path and Regulatory Science Initiatives, Office of the Commissioner, FDA
- Federico Goodsaid, PhD, VP Strategic Regulatory Intelligence, Vertex Pharmaceuticals
- James Hickman, PhD, Professor, University of Central Florida (AIMBE Fellow)
- Chris Kelley, PhD, Director, Division of Discovery Science and Technology, NIBIB, NIH (AIMBE Fellow)
- Anne Plant, PhD, Division Chief, Biosystems and Biomaterials Division, NIST (AIMBE Fellow)
- Danilo Tagle, PhD, Associate Director for Special Initiatives, NCATS, NIH

The committee decided to hold the next workshop on November 6-7, 2013 on the NIH Campus. The focus of the next workshop will be on safety and toxicity and the two workshops following that will focus on efficacy and then on biologics. The committee has begun to draft an agenda for the 4th workshop and it will include more representation from Industry and NCATS as recommended in the survey results. There will also be more representation from the toxicology community since that is the major theme of the next workshop. We hope to engage representatives from the National Toxicology Program ntp.niehs.nih.gov/ including Tox 21 and ICCVAM. We have also been successful in engaging the FDA to a greater extent and will have more FDA representation on the agenda for the next workshop. A draft agenda is amended to this report.

Agenda

Fourth Workshop on Validation and Qualification of New In Vitro Tools and Models for the Pre-Clinical Drug Discovery Process

November 6-7, 2013
Lister Hill Auditorium, NIH Campus, Bethesda, MD

November 6 Day 1

8:00-8:30 AM **Continental Breakfast and Check-In**

8:30-8:45 AM **Welcome from AIMBE and Goals of the Workshop**
James Hickman, PhD, AIMBE Fellow and Professor, University of Central Florida

8:45-9:00 AM **Welcome from the AIMBE President**
William A. Hawkins III, MBA, CEO, Immucor, Incorporated

Session 1: **Current Government Perspectives on Validation and Qualification for Toxicology**
9:00-9:10 AM *Moderator: Chris Kelley, Ph.D., AIMBE Fellow and Director, Division of Discovery Science & Technology, NIBIB/NIH*

9:10-9:25 AM **NIBIB Welcome**
Roderic Pettigrew, PhD, MD, Director NIBIB

9:25-9:45 AM **FDA Regulatory Science Perspective**
Frank Weichold, MD, PhD, Acting Director, Critical Path and Regulatory Science Initiatives

9:45-10:15 AM **New Directions for Toxicology, Testing and ICCVAM**
Linda Birnbaum, PhD, DABT, ATS, Director, NIEHS

10:15-10:45 AM ***Break***

10:45-11:15 AM **NCATS Persopective and Tox-21 Program**
Christopher P. Austin, M.D., Director, NCATS

11:15-11:45 PM **NIEHS ICCVAM Overview and New Directions**
Warren Casey, PhD, DABT, Acting Director NICEATM

11:45-1:00 PM ***Lunch***

Session 2: **Perspectives for Validation and Qualification from the Regulatory and Science Community**

1:00-1:15 PM **Perspectives for Validation and Qualification from the Regulatory and Science Community**
Khaled Abd-Elmoniem Ahmed, Staff Scientist, DHHS, NIH, NIDDK, DIR, BMIB

1:15-1:35 PM **EMA Update on ICH**
Sonja Beken, PhD, Belgian Federal Agency for Medicines and Health and the European Medicines Agency

1:35-2:05 PM **FDA Evaluation Perspective on New In Vitro Toxicology Testing System**
David Jacobson-Kram, Ph.D., DABT, Associate Director for Pharmacology & Toxicology, CDER, FDA

2:05-2:35 PM **ECVVAM Overview**
Speaker TBD

2:35-3:05 PM ***Break***

3:05-3:35 PM **Industry Perspective #1**
Frank Sistare, Merck

3:35-4:05 PM **Industry Perspective #2**
Steve Spanlahk, J&J

4:05-4:35 PM **Detailed Validation Criteria from NIST Perspective**
Anne Plant, Ph.D., Division Chief, Biosystems and Biomaterials Division, NIST

4:35-5:05 PM **CBER's View on the New Technologies.**
Richard McFarland, MD, Director for Policy, Office of Cellular, Tissue and Gene Therapies, CBER, FDA

5:05-5:35 PM **Group Discussion and Plans for Day 2**

6:00-8:00 PM **AIMBE Sponsored Reception - Share Wine Lounge (Spring 13)**
Doubletree Hotel at 8120 Wisconsin Avenue, Bethesda, Maryland 20814

November 7 Day 2

8:00-8:15 AM **Continental Breakfast**

Session 3: **Development of Draft Validation Guidelines (Spring 13)**
8:15-8:30 AM *Moderator: Anne Plant, Ph.D., Division Chief, Biosystems and Biomaterials Division, NIST*

8:30-9:00 AM **Technologies Used by the FDA for Toxicology Research**
William Slikker, Jr., Ph.D., Director, National Center for Toxicological Research

9:00-9:30 AM **Technology #1**
TBD

9:30-10:00 AM ***Break***

10:00-10:30 AM **Technology #2**
TBD

10:30-11:00 PM **Technology #3**
TBD

11:00-11:30 AM **Technology #4**
TBD

11:30-12:00 PM **Technology #5**
TBD

12:00-1:00 PM ***Lunch***

Session 4: **Parallel Breakout Sessions (Natcher, Rooms A, D, and F)**
1:00-3:00 PM **Discussion of Technology Platform #1 (Natcher, Room D)**
Presentation Leader – TBD

Discussion of Technology Platform #2 (Natcher, Room A)
Presentation Leader - TBD

Discussion of Technology Platform #3 (Natcher, Room F)
Presentation Leader – TBD

3:00-3:30 PM ***Break***

3:30-3:45 PM **Breakout Group 1 Report**
Presentation Leader – TBD

3:45-4:00 PM **Breakout Group 2 Report**
Presentation Leader – TBD

4:00-4:15 PM **Breakout Group 3 Report**
Presentation Leader – TBD

4:15-5:00 PM **Final Discussion**
Further development of validation and qualification guidelines for microphysiological systems. These guidelines will be used by the steering committee to meet with the FDA to determine next steps based on FDA requirements and to set the agenda for the next workshop

5:00 PM **Adjourn**